Metabolic Surgery for Type 2 Diabetes - Window into Pathophysiology-

Prof. Francesco Rubino, MD

Chair of Bariatric and Metabolic Surgery
King's College London
London, UK

September 15, 2014

DISCLOSURE SLIDE

- NGM Biopharmaceuticals (SAB Member)
- Fractyl Laboratories (Advisor/Consultant)

Surgery and Physiology

Surgical manipulations of anatomy have played a major role in advancing knowledge about physiology and disease

Surgery has helped advance understanding the functioning of:

- Central nervous system
- Pituitary gland
- Adrenals
- Pancreas

Bariatric Surgery and Metabolic Disease

“criteria ex juvantibus”

making an inference about disease causation from observations on the response of the disease to a treatment

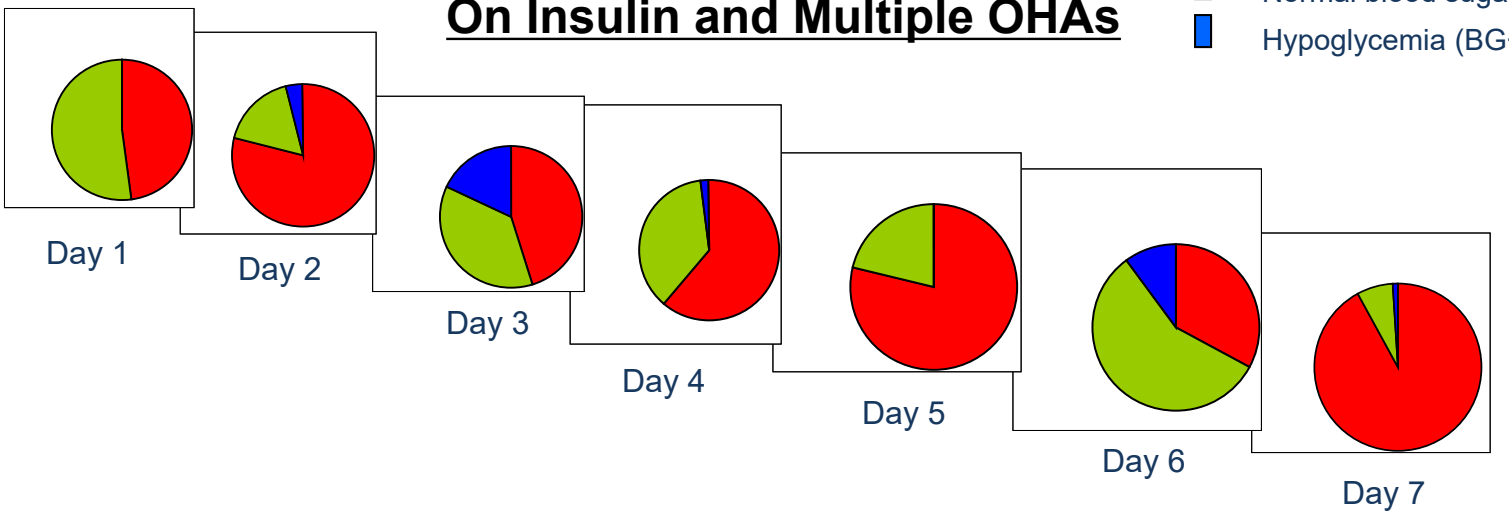
Surgical Treatment of Type 2 Diabetes:

Clinical Outcomes

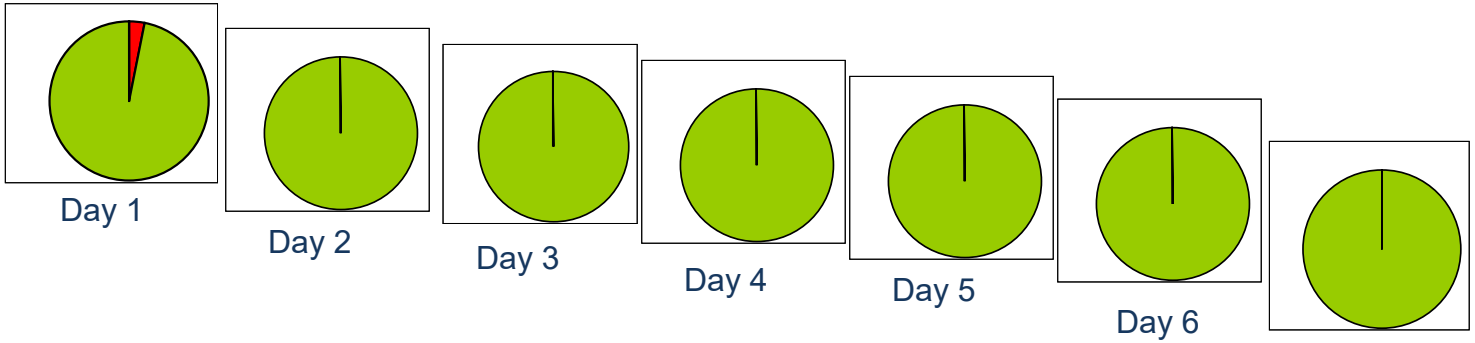
Preoperative

Female, 42yo, BMI 31
On Insulin and Multiple OHAs

Hyperglycemia (BG>180mg/dl)
Normal blood sugar (BG btwn 70-180)
Hypoglycemia (BG<70mg/dl)



2 Weeks after RYGB Blood Glucose Levels



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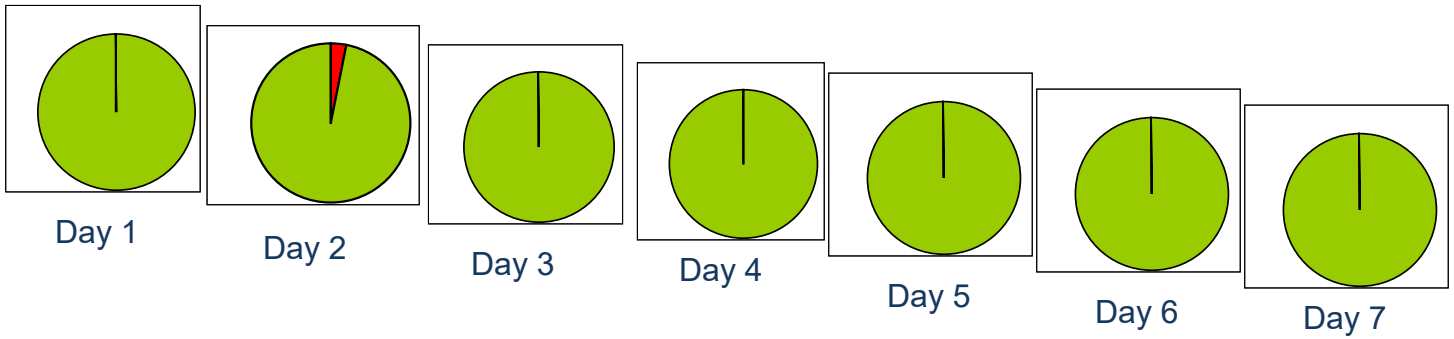
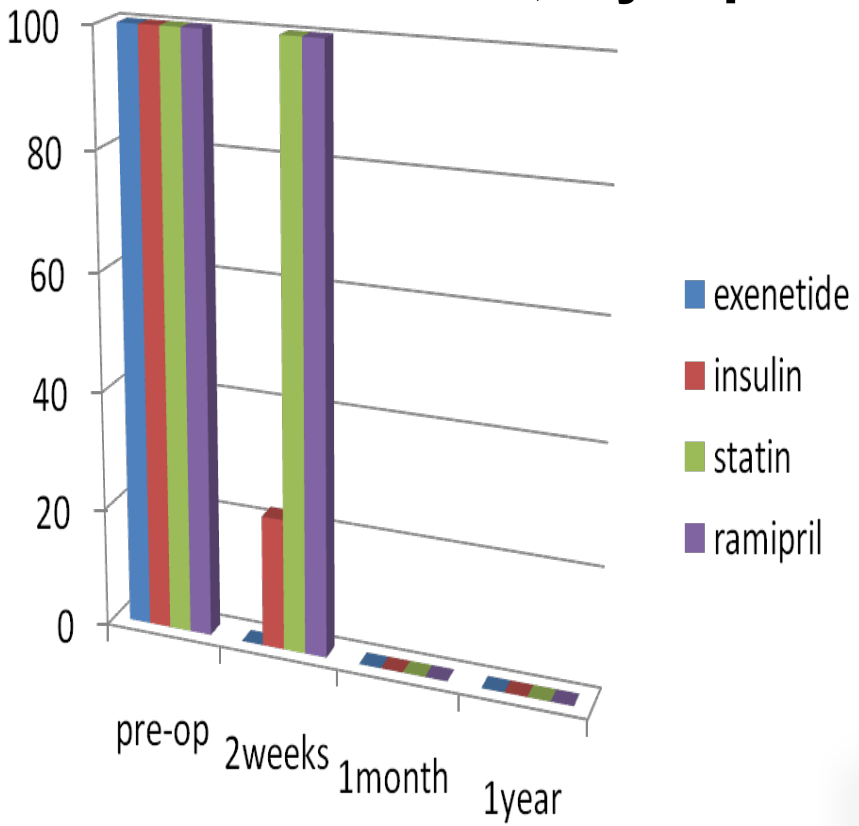
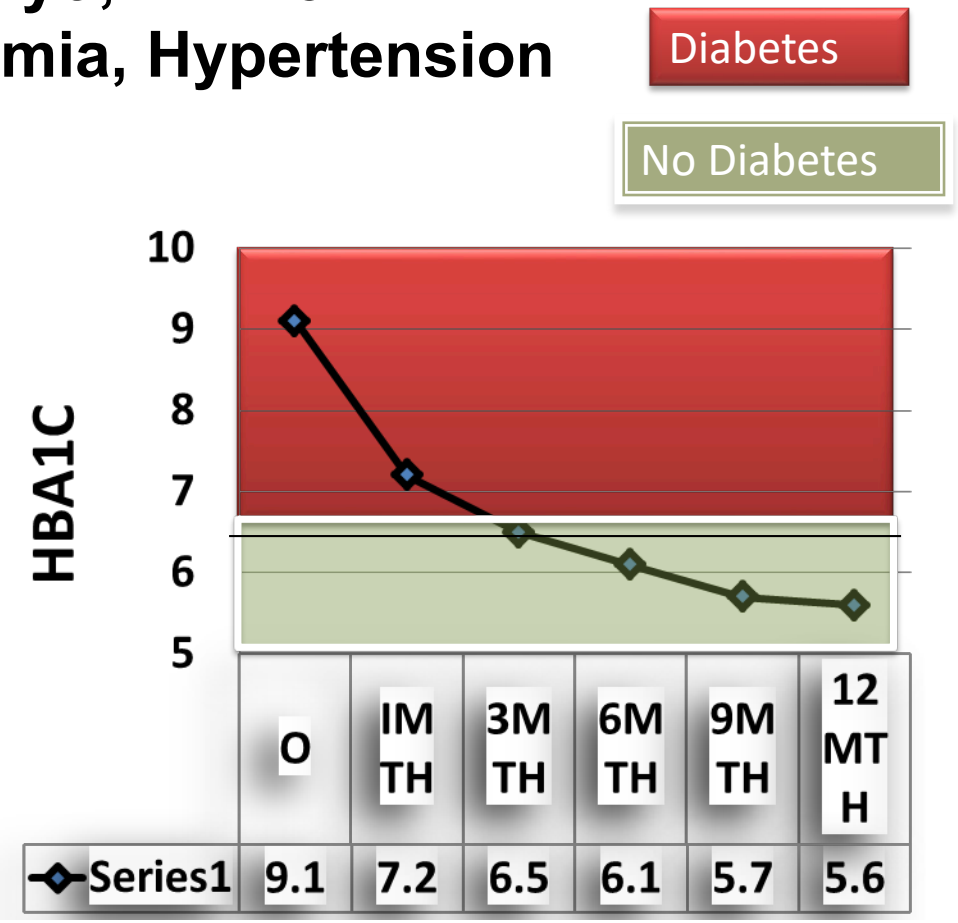


An Instructive Case:

Female, 42yo; BMI: 31
T2DM; Dyslipidemia, Hypertension





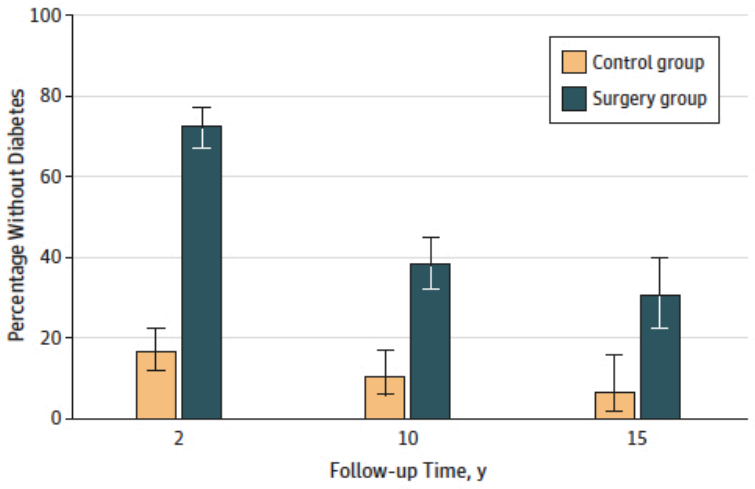
Original Investigation

Association of Bariatric Surgery With Long-term Remission of Type 2 Diabetes and With Microvascular and Macrovascular Complications

JAMA, June 2014

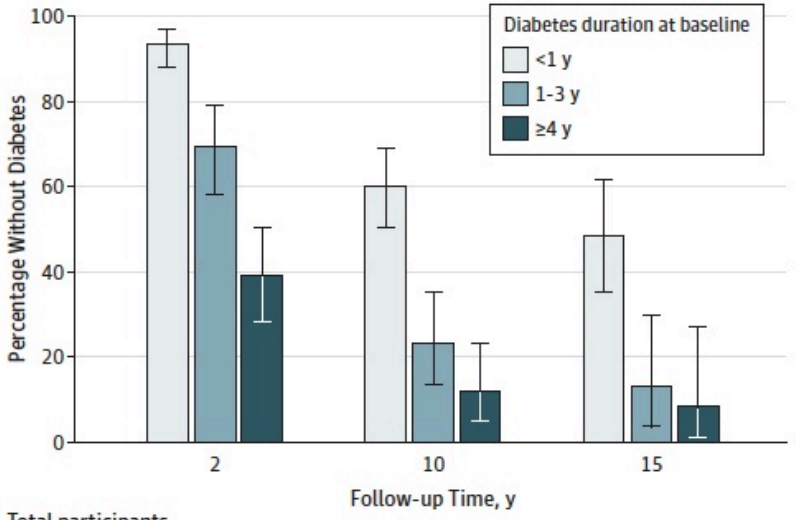
Lars Sjöström, MD, PhD; Markku Peltonen, PhD; Peter Jacobson, MD, PhD; Sofie Ahlin, MD, PhD; Johanna Andersson-Assarsson, PhD; Åsa Anveden, MD; Claude Bouchard, PhD; Björn Carlsson, MD, PhD; Kristjan Karason, MD, PhD; Hans Lönroth, MD, PhD; Ingmar Näslund, MD, PhD; Elisabeth Sjöström, MD; Magdalena Taube, PhD; Hans Wedel, PhD; Per-Arne Svensson, PhD; Kajsa Sjöholm, PhD; Lena M. S. Carlsson, MD, PhD

Figure 1. Prevalence of Diabetes Remission in the Bariatric Surgery and Control Groups



Total participants			
Control	207	135	62
Surgery	303	236	115
Odds ratio (95% CI)	13.3 (8.5-20.7)	5.3 (2.9-9.8)	6.3 (2.1-18.9)

Figure 2. Diabetes Remission by Diabetes Duration in the Surgery Group



Total participants			
<1 y	139	113	60
1-3 y	82	65	31
≥4 y	82	58	24

Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials

BMJ Oct 22, 2013

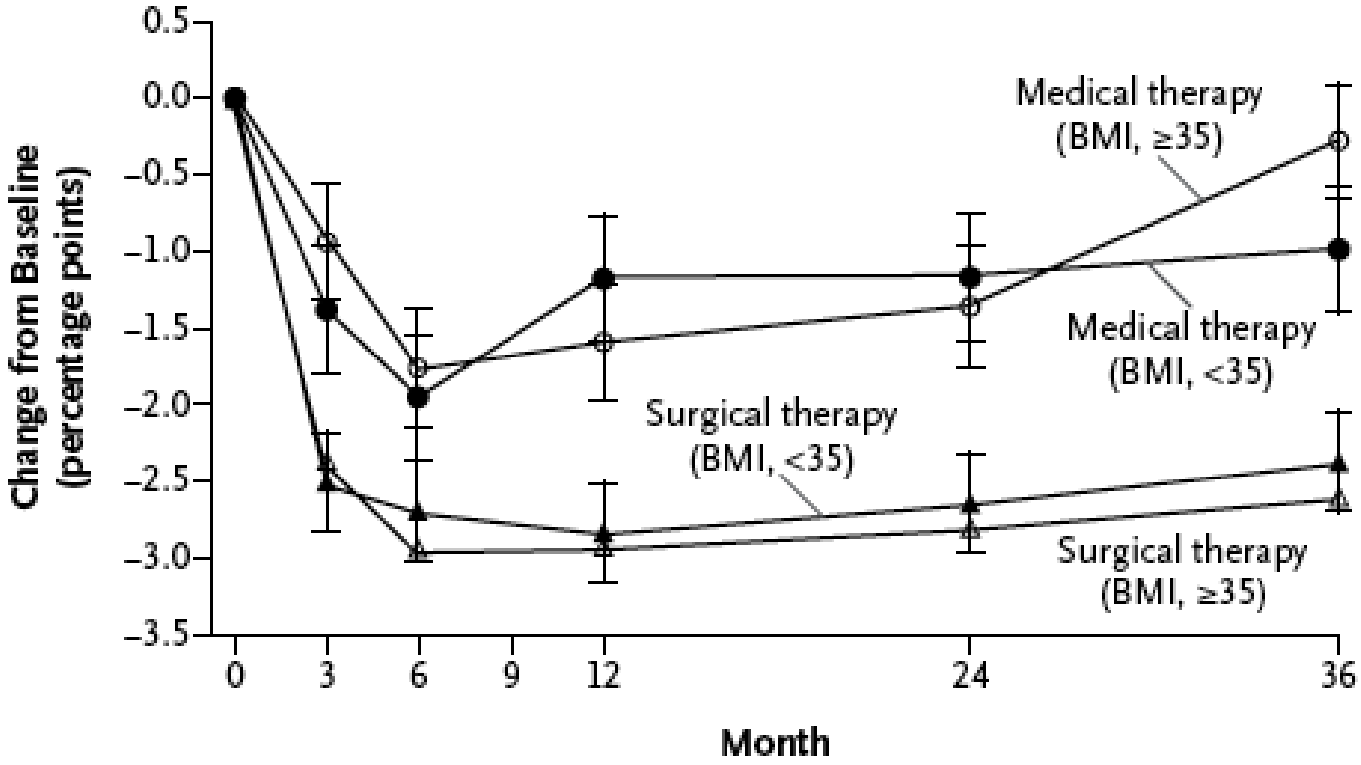
Viktoria L Gloy *junior researcher*[1], Matthias Briel *assistant professor*[1 2], Deepak L Bhatt *professor*[3], Sangeeta R Kashyap *associate professor of medicine*[4], Philip R Schauer *medical director, professor of surgery*[5], Geltrude Mingrone *professor*[6], Heiner C Bucher *director*[1], Alain J Nordmann *associate professor*[1]

Study
Mingrone 2012[36]
Schauer 2012[18]
Reis 2010[20]
Ikramuddin 2013[19]
Liang 2013[24]
O'Brien 2006[23]
O'Brien 2010[21]
Dixon 2008[25]
Dixon 2012[22]
Mingrone 2002[17]
Heindorff 1997[26]

- 11 studies, 796 patients, BMI 27-53
- Surgery superior to med Rx
  - Wt. loss, HbA1c, T2DM remission, TG, HDL, remission of metabolic syndrome, QOL, medication reduction
- No CV events or death after surgery
- Anemia (15%), Reoperation (4-8%)

BMI < 35 vs. BMI ≥ 35
Change in HbA1c

B **Glycated Hemoglobin According to Body-Mass Index**



Value at Visit					
Medical <35 BMI	9.1 (8.9)	7.2 (6.8)	7.9 (6.9)	8.0 (7.4)	8.1 (7.8)
Medical ≥35 BMI	8.8 (8.5)	7.1 (6.8)	7.2 (6.7)	7.4 (6.9)	8.5 (7.3)
Surgical <35 BMI	9.4 (9.1)	6.7 (6.9)	6.6 (6.6)	6.8 (6.8)	7.1 (6.7)
Surgical ≥35 BMI	9.3 (9.2)	6.4 (6.2)	6.4 (6.1)	6.6 (6.4)	6.7 (6.4)

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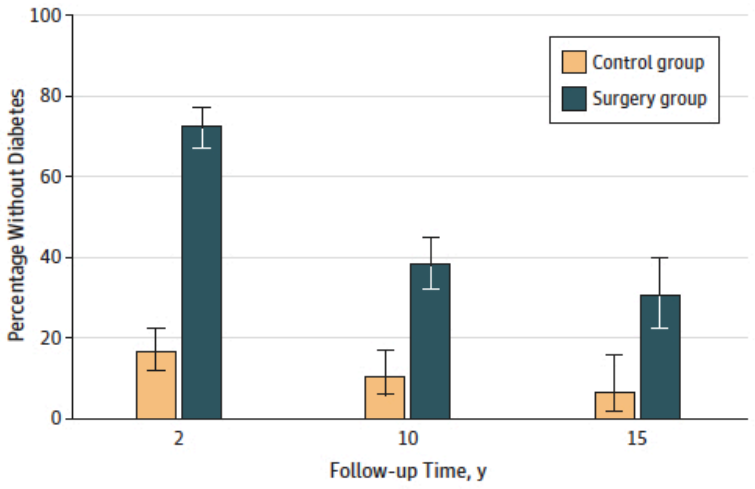

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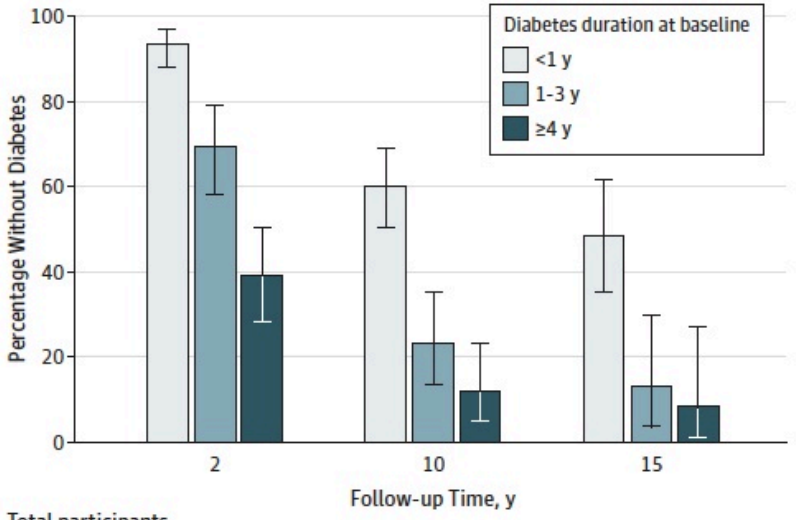

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STAMPEDE Trial: QoL Changes

- Gastric Bypass: 5/8 domains improved
- Sleeve Gastrectomy: 2/8 domains improved
- Intensive Med Rx: 0/8 domains improved

Schauer et al. NEJM 2014

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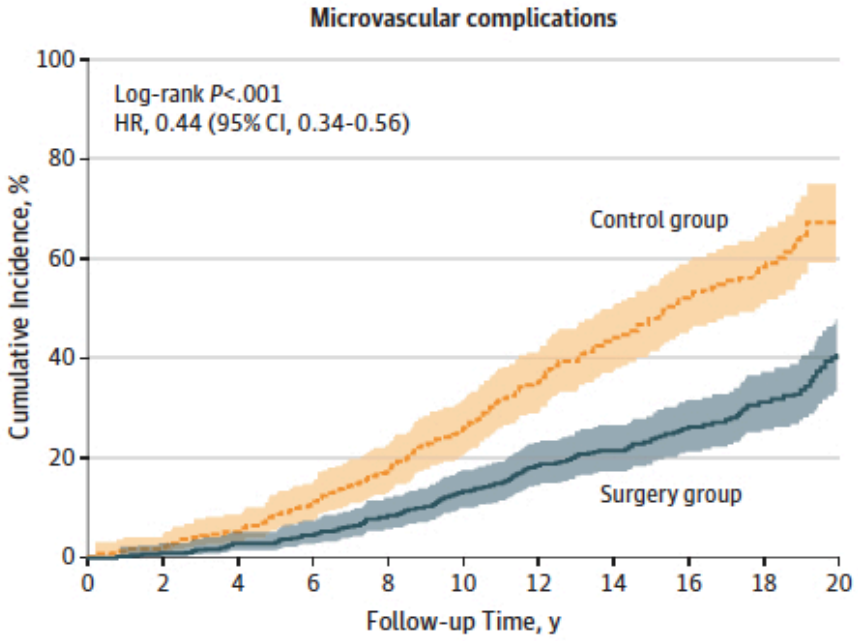
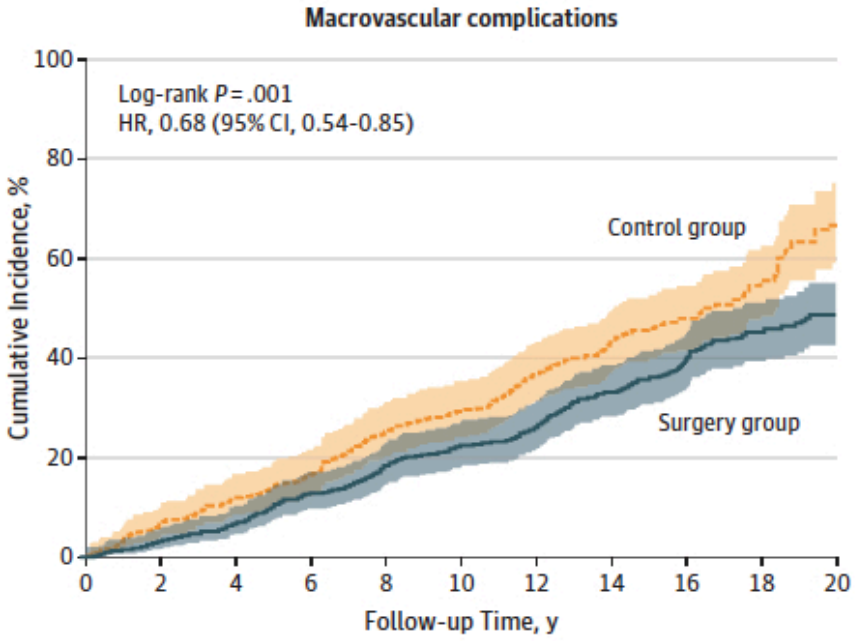
Figure 3. Cumulative Incidence of Microvascular and Macrovascular Diabetes Complications in the Surgery and Control Groups

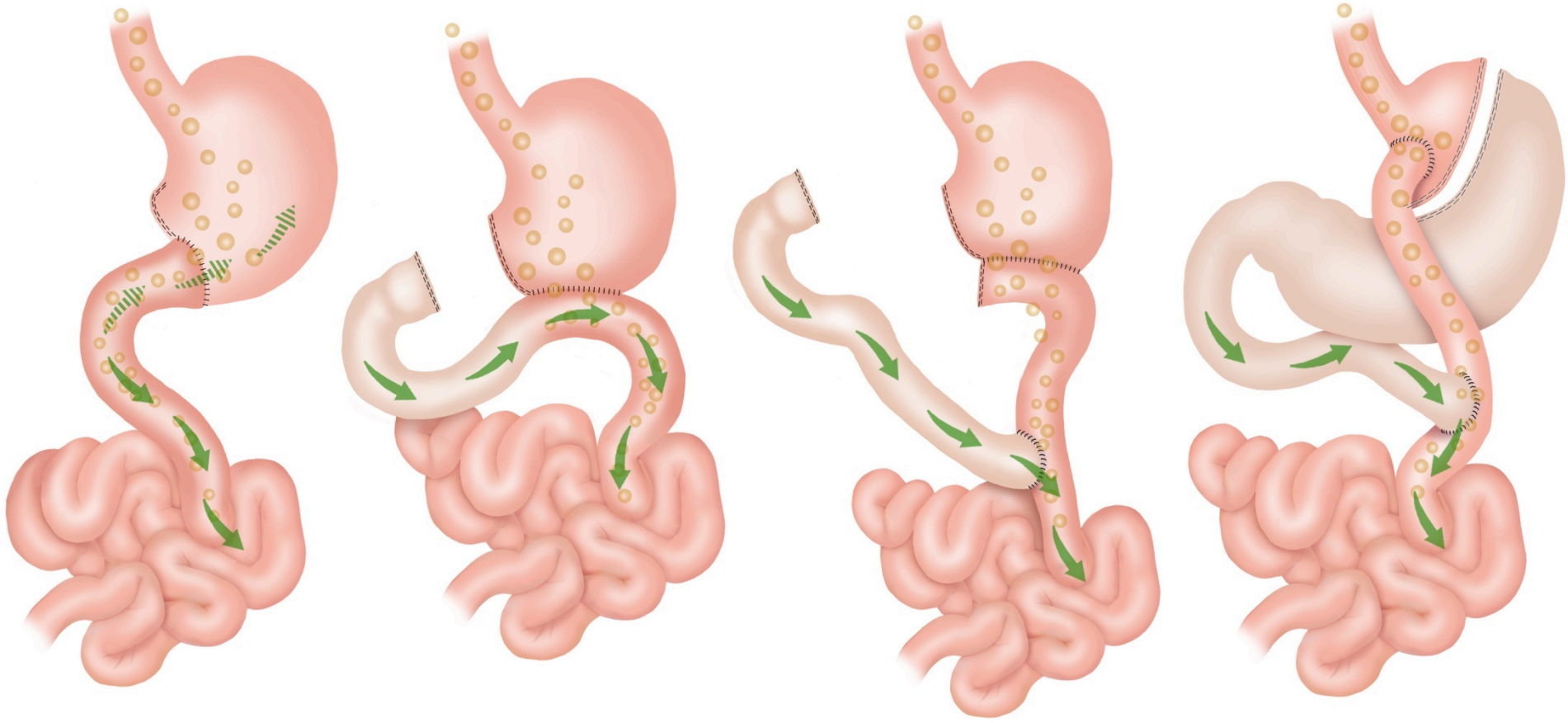




Bariatric Surgery Associated With Reduced Long-Term, All-Cause Mortality Compared With Non-Operated Controls

Study	Procedure	F/U	Mortality Reduction
MacDonald, 1997	RYGB	9 yr	88%
Flum, 2004	RYGB	4.4 yr	33%
Christou, 2004	RYGB	5 yr	89%
Sowemimo, 2007	RYGB	4.4 yr	63%
Dixon, 2007	LAGB	12 yr	72%
Adams, 2007	RYGB	8.4 yr	40%
Sjostrom, 2007	VBG/other	14 yr	31%
Perry, 2008	RYGB/LAGB	2 yr	48%

Is there something special in the mechanism of action of bariatric surgery ?


BI Gastrectomy
BII-Gastrectomy
RY-Gastrectomy
RYGB

DIABETES AND OPERATION.

A NOTE ON THE EFFECT OF GASTRO-JEJUNOSTOMY UPON A CASE OF MILD DIABETES MELLITUS WITH A LOW RENAL THRESHOLD.

BY O. LEYTON, M.D. CAMB., F.R.C.P. LOND.,
PHYSICIAN TO THE LONDON HOSPITAL.

How can we account for the apparent improvement? The glycosuria was absent after operation in spite of a diet containing a fair amount of carbohydrate. In order to determine whether the operation

THE AMELIORATION OF DIABETES MELLITUS FOLLOWING SUBTOTAL GASTRECTOMY

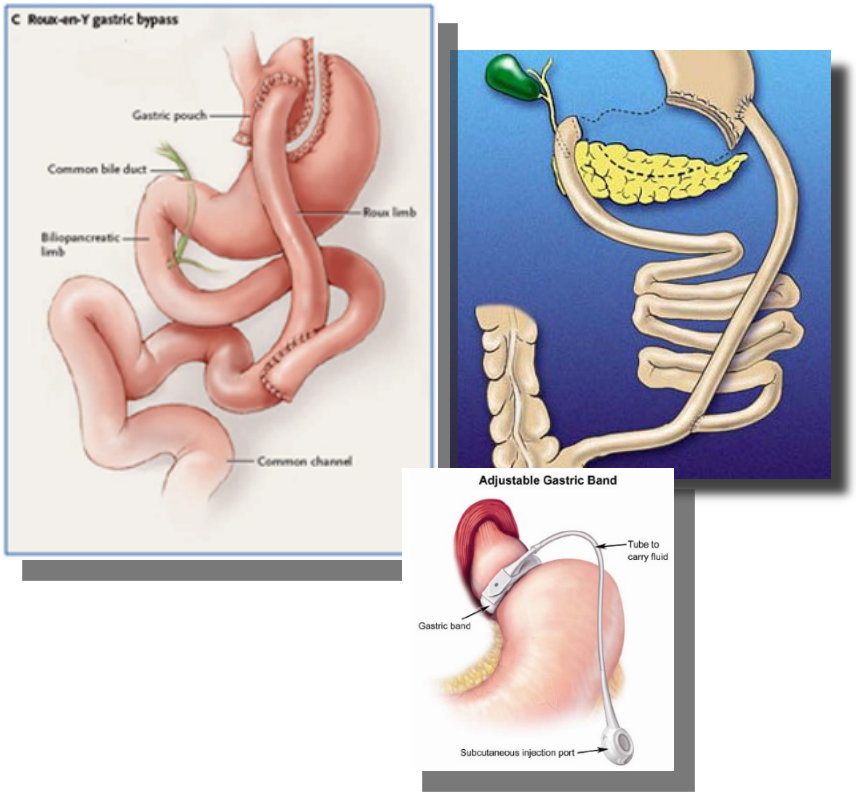
MURRY N. FRIEDMAN, M.D., F.A.C.S., ANTONIO J. SANCETTA, M.D., and GEORGE J. MAGOVERN, M.D., Brooklyn, New York

1955

IN 1923, MURLIN noted the presence of a substance in extracts of the pancreas which could raise the blood sugar. Subsequently, this hyperglycemic factor was demonstrated

and duodenum. Therefore, when subtotal gastrectomy for duodenal ulcer resulted in marked amelioration of the diabetic state in 3 patients at the Brooklyn Veterans Hospi-

Reports of Diabetes Remission after Bariatric Surgery Procedures



- Jejuno-ileal bypass
  - Ahmad et al; Diabetes Care 1978
  - Ackerman NB. Surg Gynecol Obstet. 1981
- Verical banded gastroplasty
  - Neve HJ et al; Obesity Surg 1993
- Biliopancreatic diversion
  - Scopinaro et al; WJS 1998
- Gastric Bypass
  - Printen et al; Am Surg 1979
  - Pories et al; Ann Surg. 1987
  - Pories et al; Ann Surg 1992

Despite surgical control of diabetes was reported since 1925, the effect (and opportunity) remained unknown to the scientific community through the XX century

- Segmentation of medical specialties in XX-century medicine
- Diabetes considered invariably chronic and progressive disease > things that cannot be explained are often looked with skepticism in medicine
- Prevailing view that obesity leads to diabetes and that weight loss improves hyperglycemia > surgical control of diabetes after bariatric surgery not enough “incongruous” to inspire new hypothesis
- For most of the XX-century the GI tract was regarded as merely a tube for digestion and absorption of nutrients
- As an implicitly organ-focused intervention, surgery could not be seen as a rational solution for a systemic disease such as diabetes.

1999

- First Protocol for a Randomized Clinical Study of Diabetes Surgery Submitted to IRB (Mount Sinai Medical Center, New York)

RCT comparing Gastric Bypass Surgery vs Intensive Medical Therapy in patients with BMI 30-35

The IRB does not approve

Effect of Duodenal–Jejunal Exclusion in a Non-obese Animal Model of Type 2 Diabetes

A New Perspective for an Old Disease

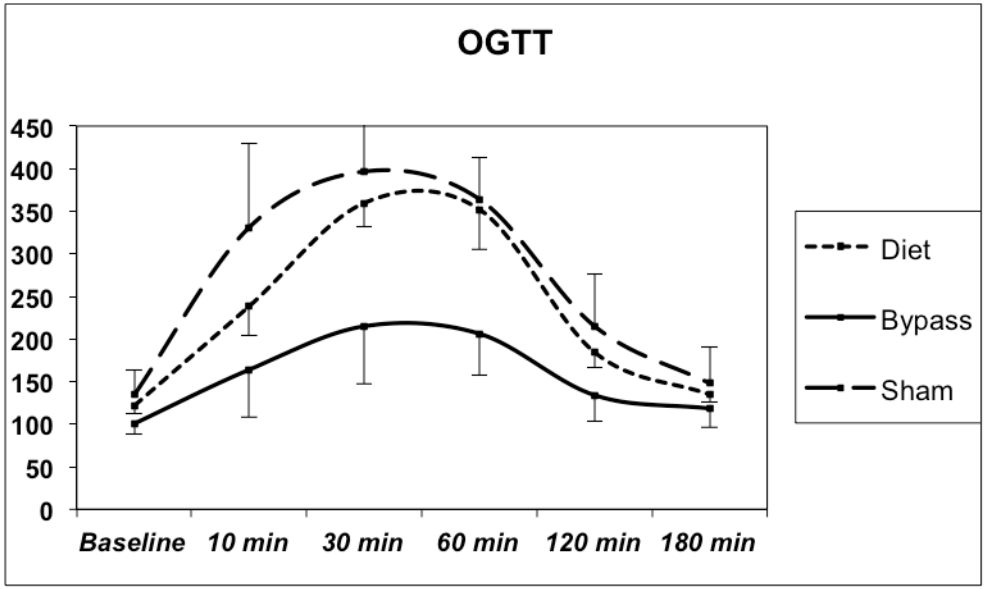
Francesco Rubino, MD, and Jacques Marescaux, MD, FRCS

Background: The Roux-en-Y gastric bypass and the biliopancreatic diversion effectively induce weight loss and long-term control of type 2 diabetes in morbidly obese individuals. It is unknown whether the control of diabetes is a secondary outcome from the treatment of

These findings suggest a potential role of the proximal gut in the pathogenesis the disease and put forward the possibility of alternative therapeutic approaches for the management of type 2 diabetes.

(*Ann Surg* 2004;239: 1–11)

GK-Rat
Lean, type 2 diabetes
Hyperinsulinism
Insulin resistance
(Nature Genetics 1996)



ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

January 2004

FEATURE

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(*Ann Surg* 2004;239: 1–11)

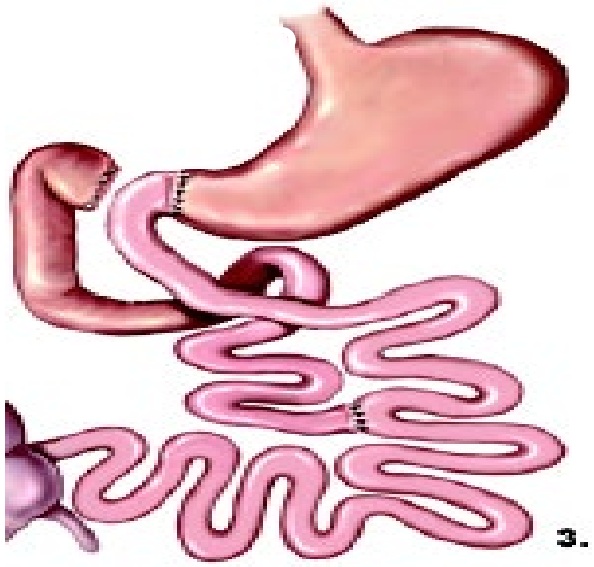
First experimental evidence that diabetes resolution is a weight-independent, direct effect of GI surgery

Rationale for DIABETES SURGERY

Gastrointestinal Bypass Improves Glucose Homeostasis in Rodents by Weight Independent Mechanisms

GK-Rat (Lean)

Rubino et al, Ann Surg 2004
Rubino et al, Ann Surg 2006
Pacheco et al, Am J Surg 2007
Cheng et al, Ann Surg 2008
Kindel et al J Gastr Surg 2009
Saberi et al (Diabetes 2013)

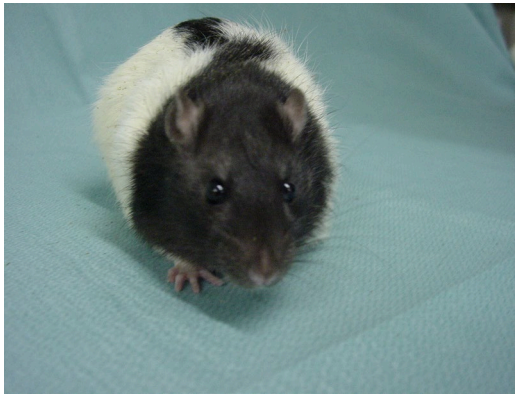


Obese mice

Troy et al, Cell Metabolism, Sept 2008

Stretptoz. Diabetes

Breen et al, Nature Med 2011



Type 1 Diabetes

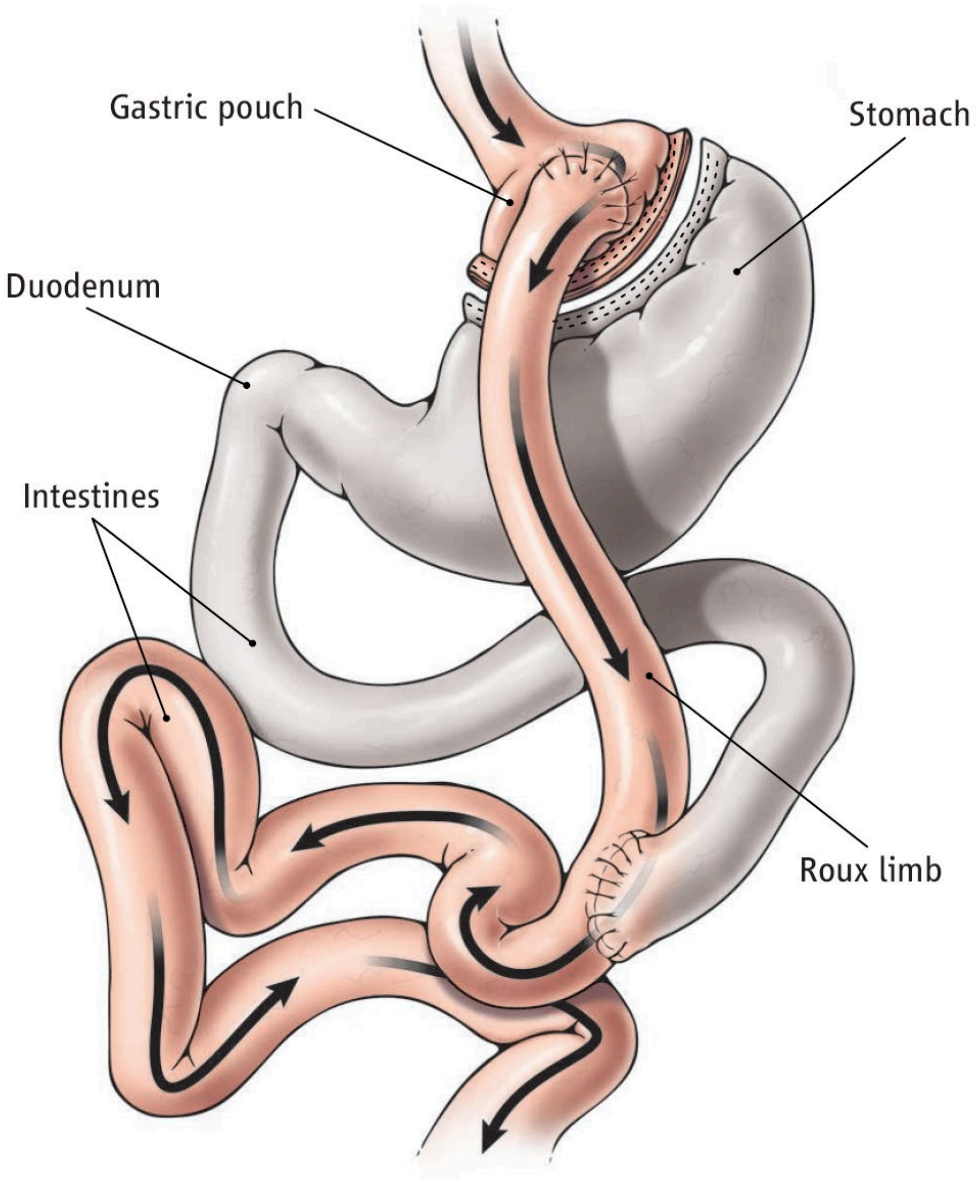
Breen et al, Nature Med 2011

Obese - Diabetic rat

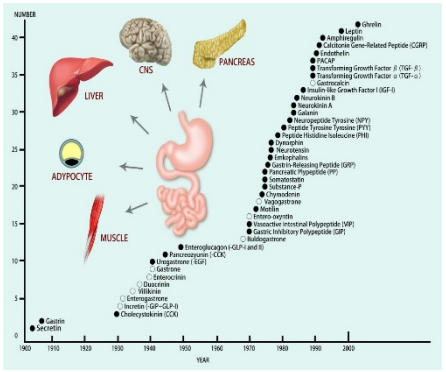
Rubino et al, Endocrinology 2005
Saberi et al, Diabetes 2013
Patel et al. Obesity 2013

Mechanisms of Action of GI Surgery 2004-2014

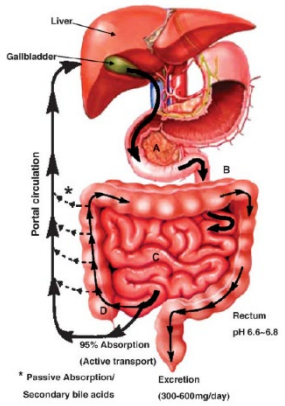
How Does Surgery work?



Mechanisms of Surgical Control of Diabetes

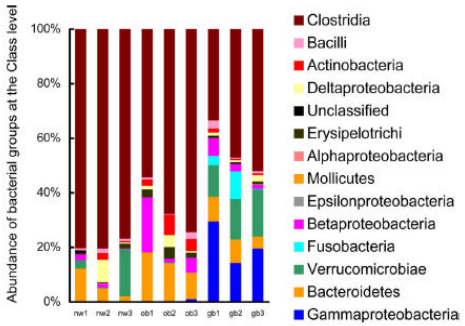


Gut Hormones

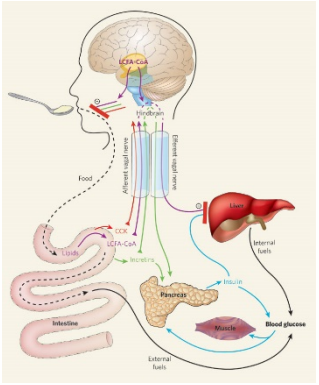


Bile Acids

-intestinal glucose re-programming (Science 2013)
-intestinal gluco-neogenesis
-others

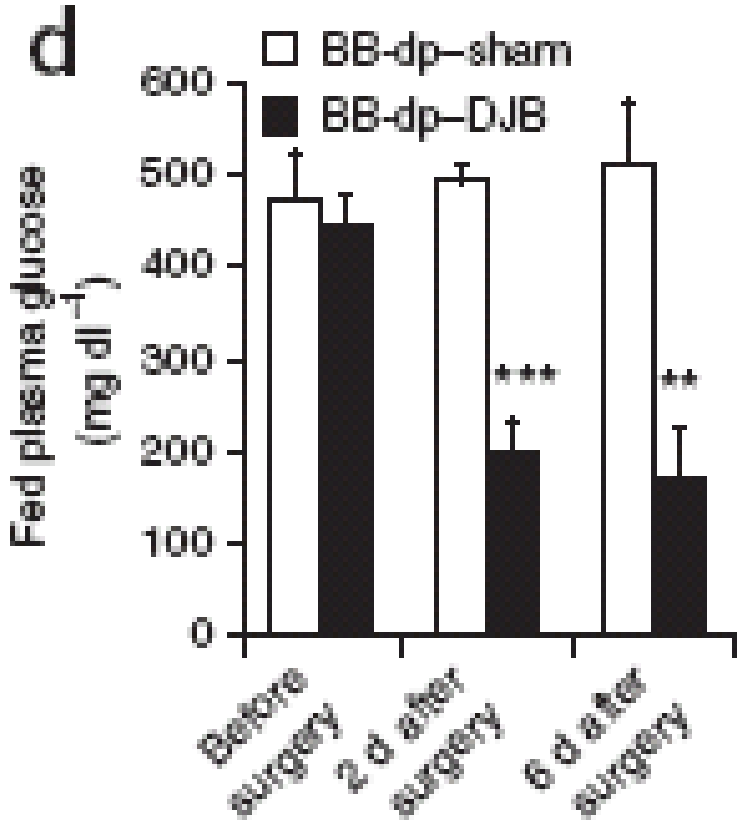


Microbiota

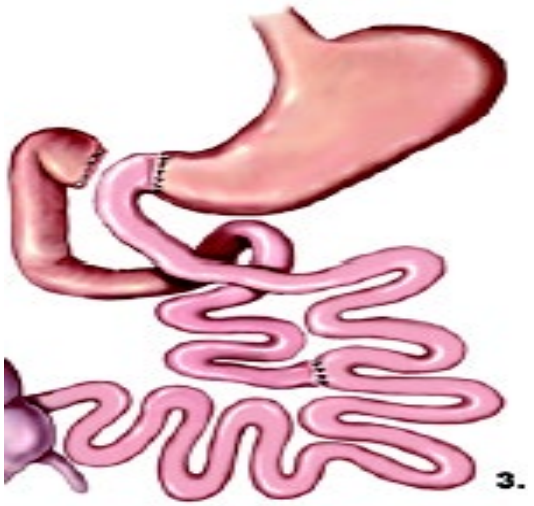


Nutrient Sensing

Glucose-lowering effect of DJB in absence of insulin



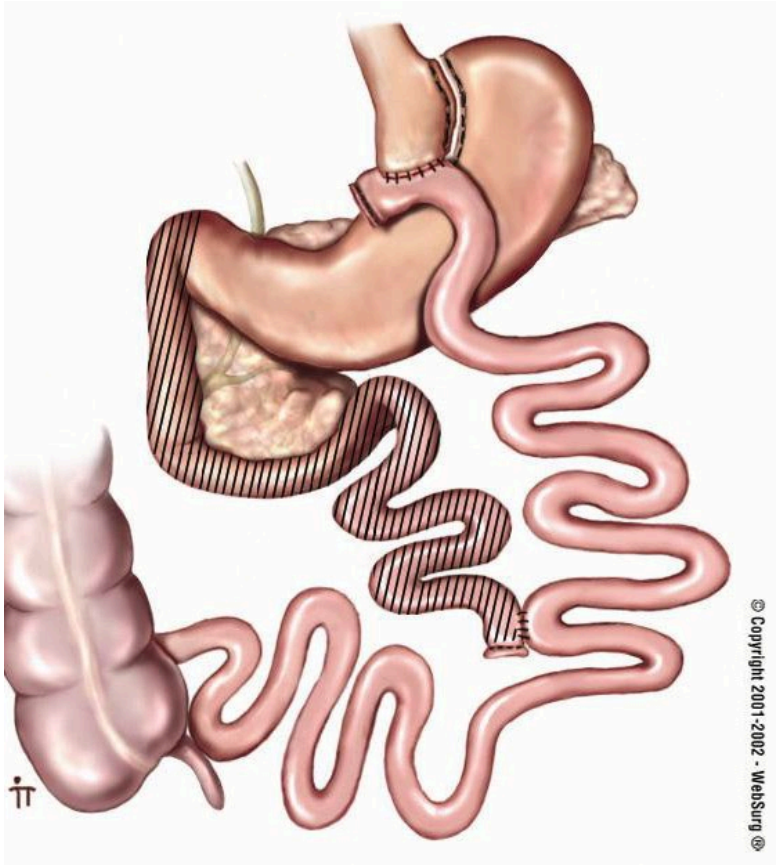
Non-obese type 1 diabetic mice

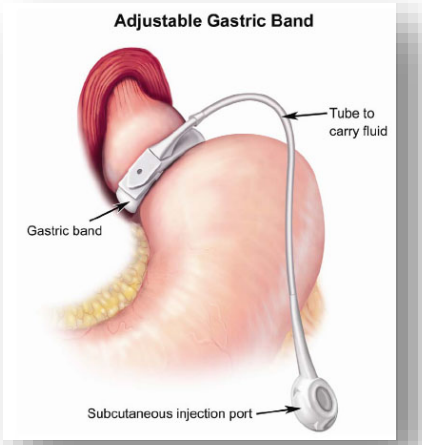


Breen *et al*.
Nature Medicine 2012

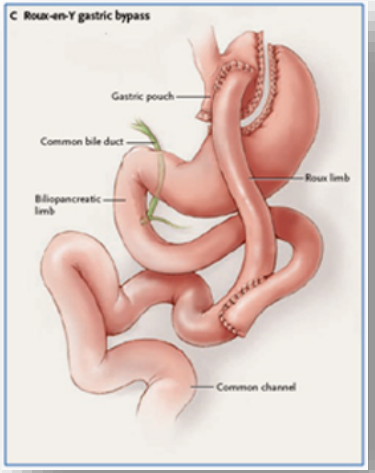
Courtesy of Dr Lee Kaplan	Gastric Band	Sleeve Gastrex	RYGB	DJB	BPD	Ileal Inter-position	Endo-luminal Sleeve
Gastric Restriction	✓	✓	✓		±		
Gastrectomy		✓			✓		
Altered gastric function	✓	✓	✓		✓		?
Gastric exclusion			✓				
Duodenal exclusion			✓	✓	✓		✓
Enhanced distal nutrient delivery			✓	✓	✓	✓	✓
Malabsorption					✓		
Partial vagotomy	±		✓		?		

Evidence for anti-diabetic effects of proximal intestinal bypass

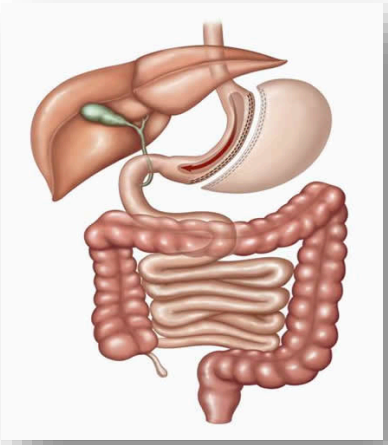




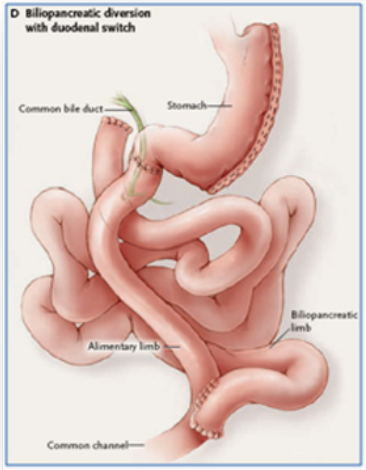
Gastric Banding



RY Gastric Bypass



Sleeve Gastrectomy

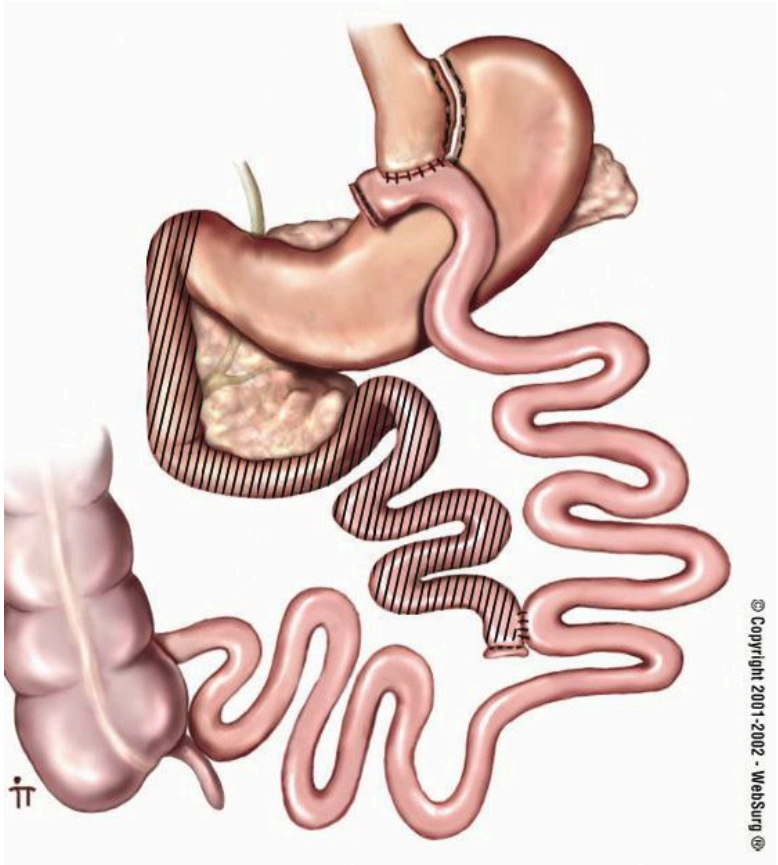


BPD

All improve Diabetes, although with different potency and likely distinct mechanisms

RCTs and clinical series suggest

Gradient BPD > RYGB > Sleeve > Banding



Lower Intestinal

vs.

Upper Intestinal

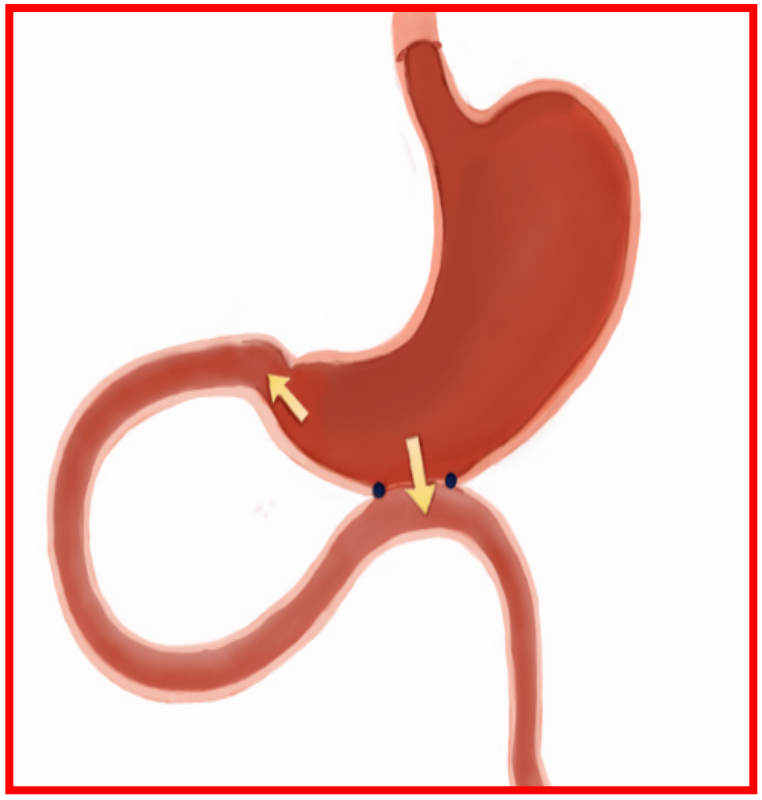
Hypothesis?

Rubino F, et al Annals of Surgery 2006

Duodenal (Jejunal) Exclusion

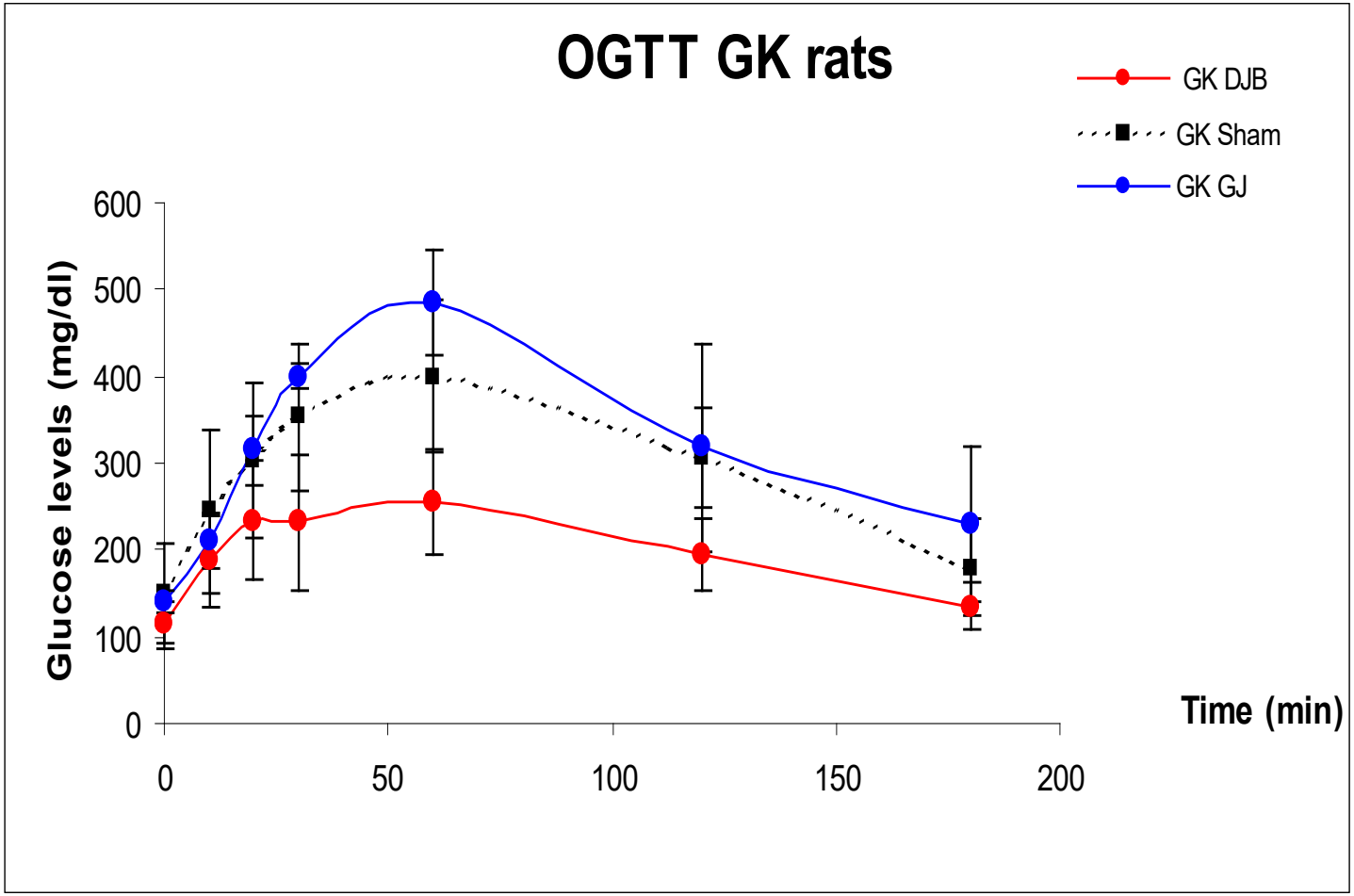
Gastro-jejunal Anastomosis

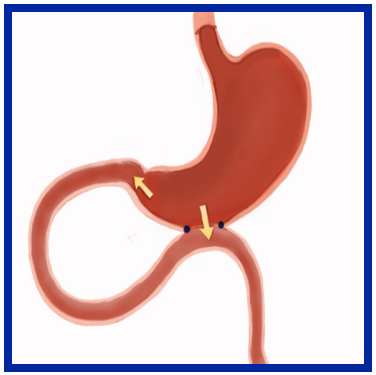
(enhanced distal delivery of nutrients)

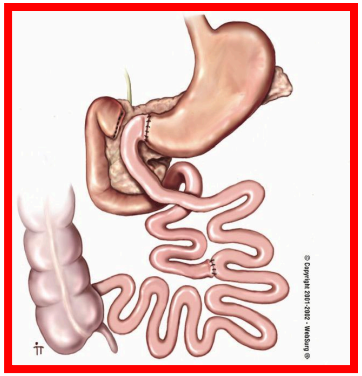


Rubino F, *et al., Ann Surg 2006;* **244:741**

G-J Anastomosis alone does not Improve Diabetes in Rats

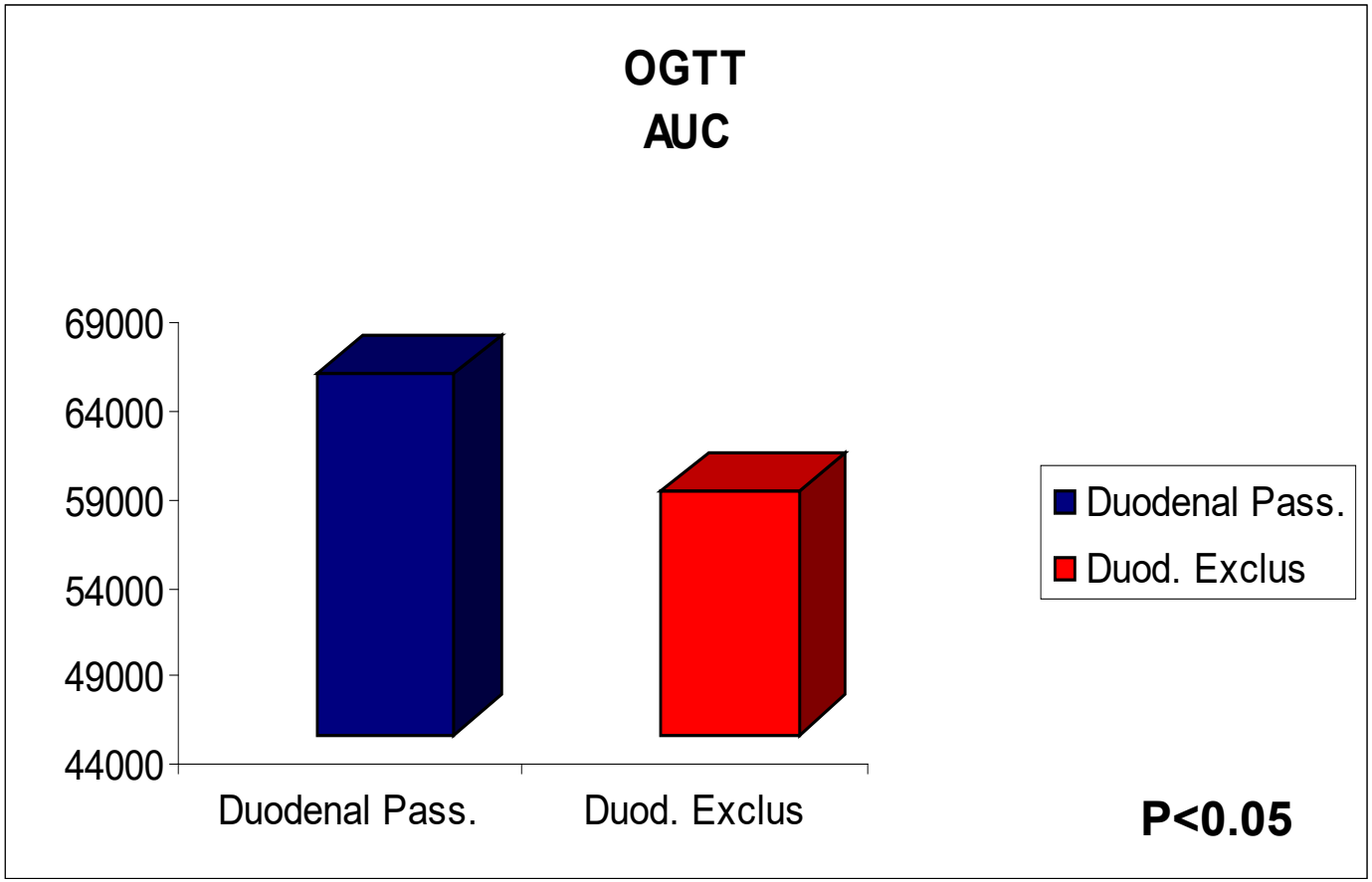


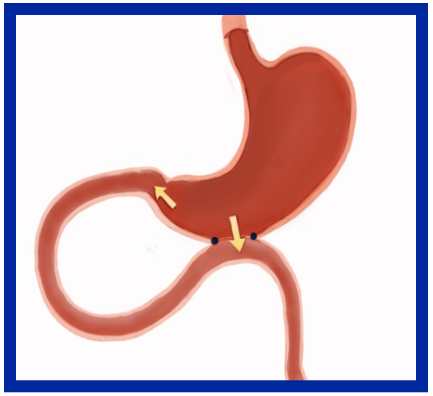


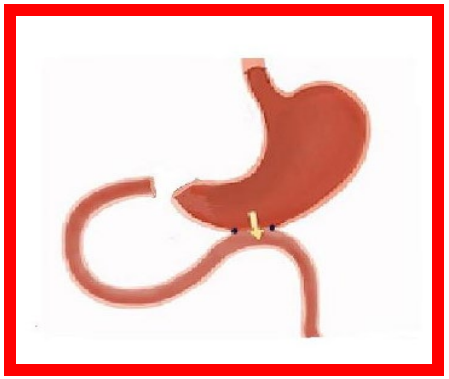


Rubino et al; Annals of Surgery Nov 2006

Adding Doudenal Exclusion to GJ improves diabetes in rats

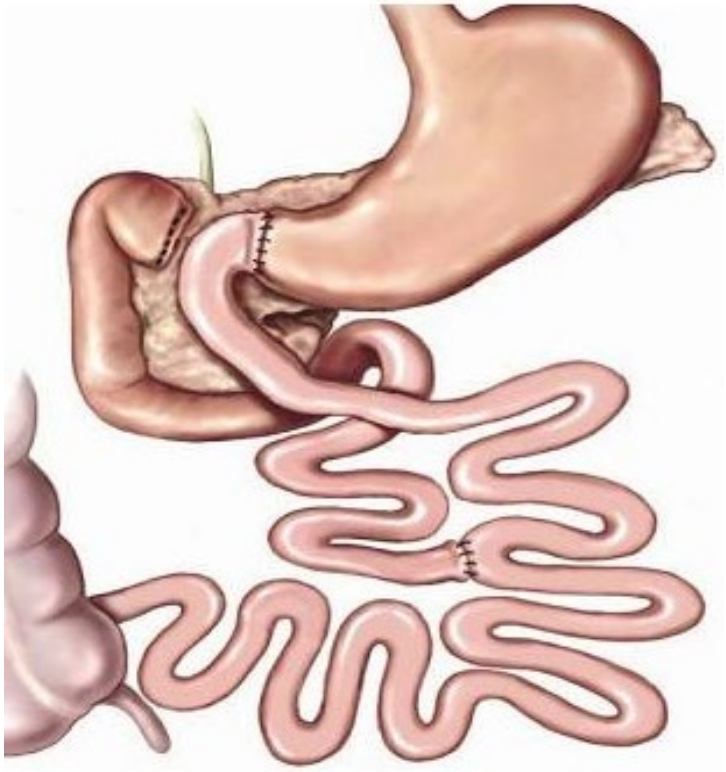






Rubino et al; Annals of Surgery Nov 2006

Restoration of Duodenal Passage after DJB worsens glucose tolerance



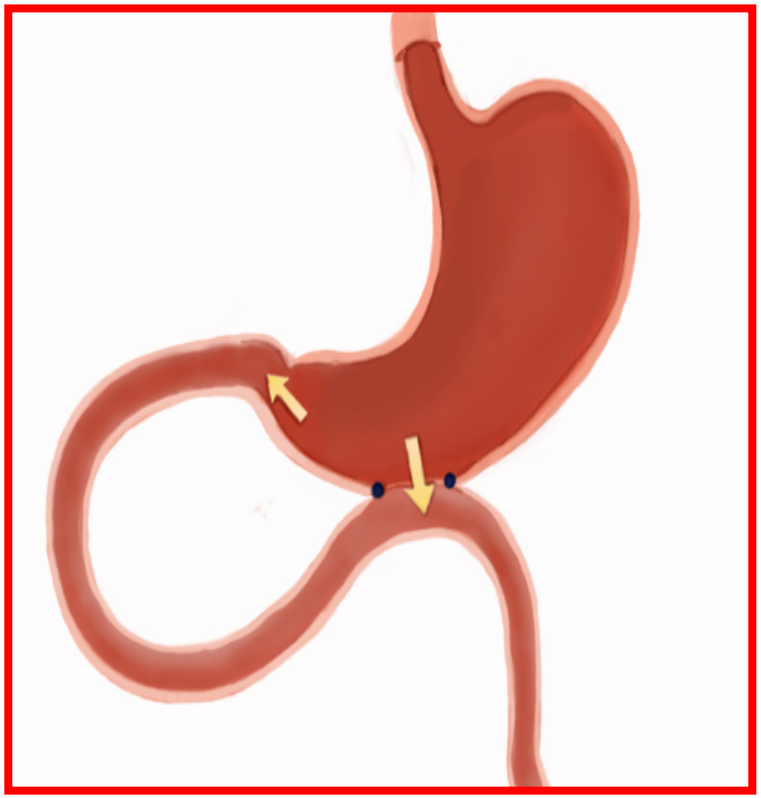
AUC OGTT X 2

Rubino et al; Annals of Surgery Nov 2006

Duodenal (Jejunal) Exclusion

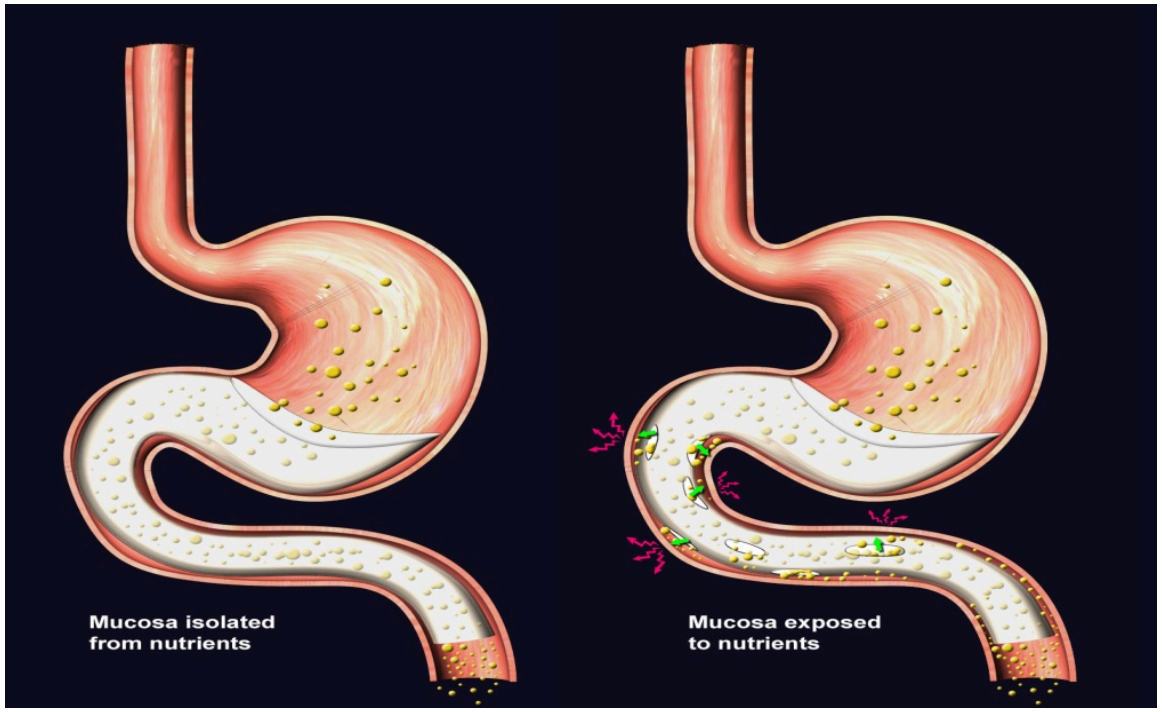
Improves DM in rats

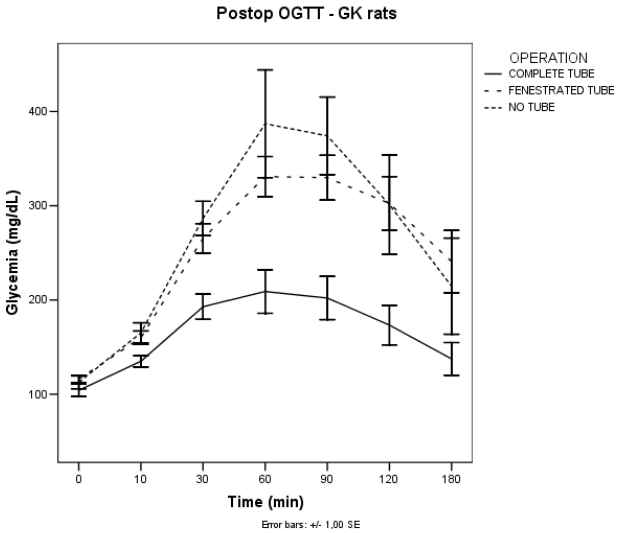
Gastro-jejunal Anastomosis



No Effect on DM in rats

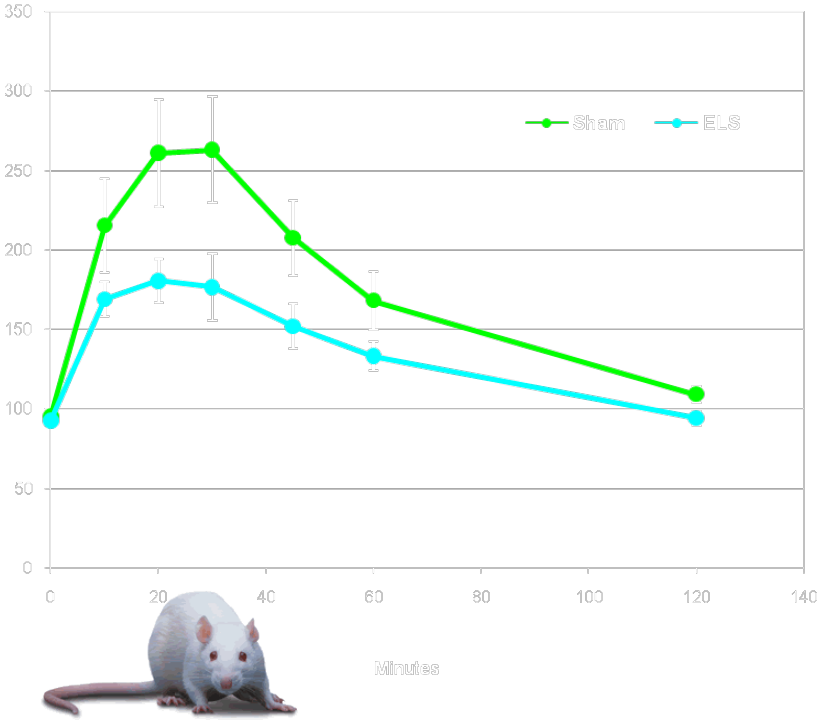
Duodenal Jejunal Exclusion has distinct anti-diabetic effects

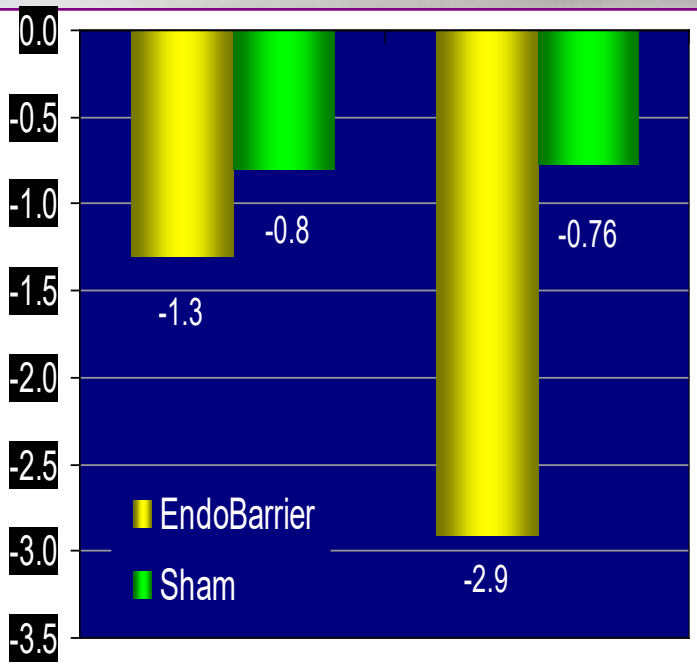




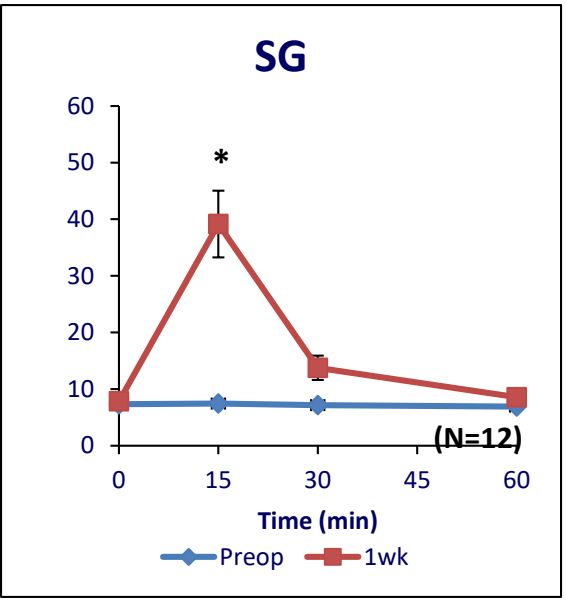
Rubino et al. Ann Rev Med 2010

ELS Improves IP Glucose Tolerance (Kaplan et al)

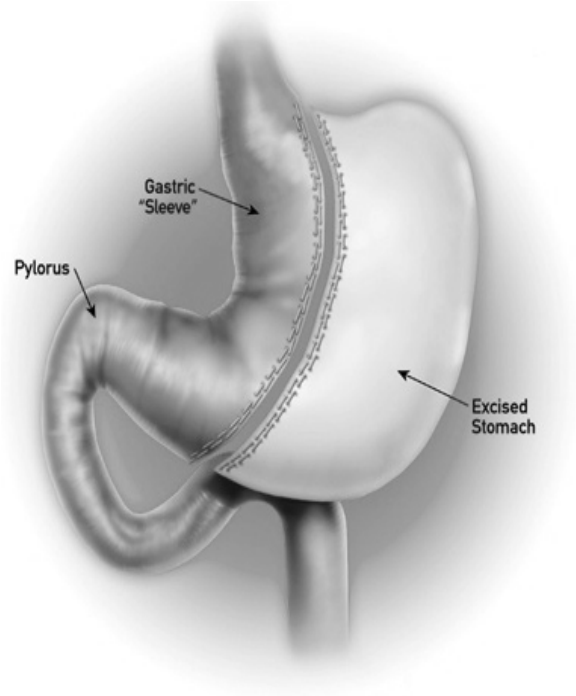




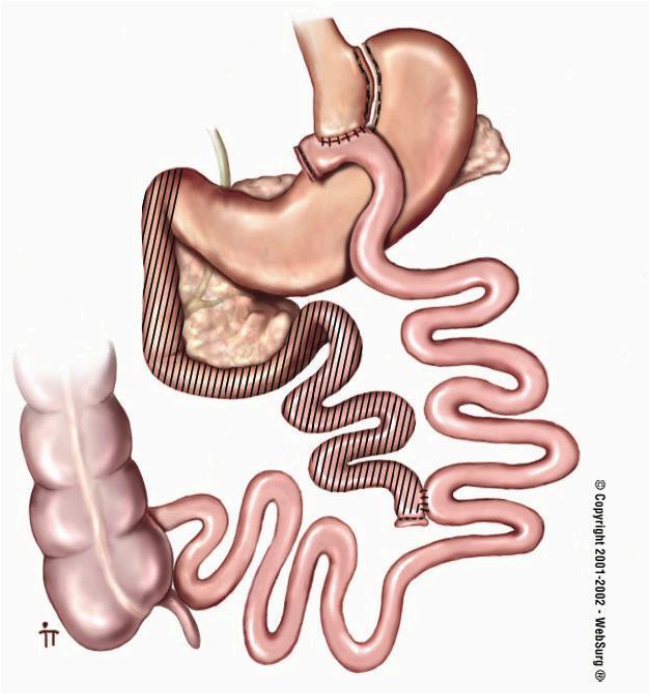
rapid rise and fall of postprandial GLP-1



Effects of SG not abolished in GLP-1R KO mice (Wilson-Perez et al; Diabetes 2013)



injection of GLP1-R Antagonist does not DOES NOT reverse improvement of diabetes in humans who had RYGB (Jimenez et al; Diabetes Care 2013)



GLP-1 not the principal mediator of Diabetes remission after bariatric surgery

Bypass of the Proximal Intestine :

How Does it Work?

Other endocrine mechanisms?

Paracrine mechanisms ?

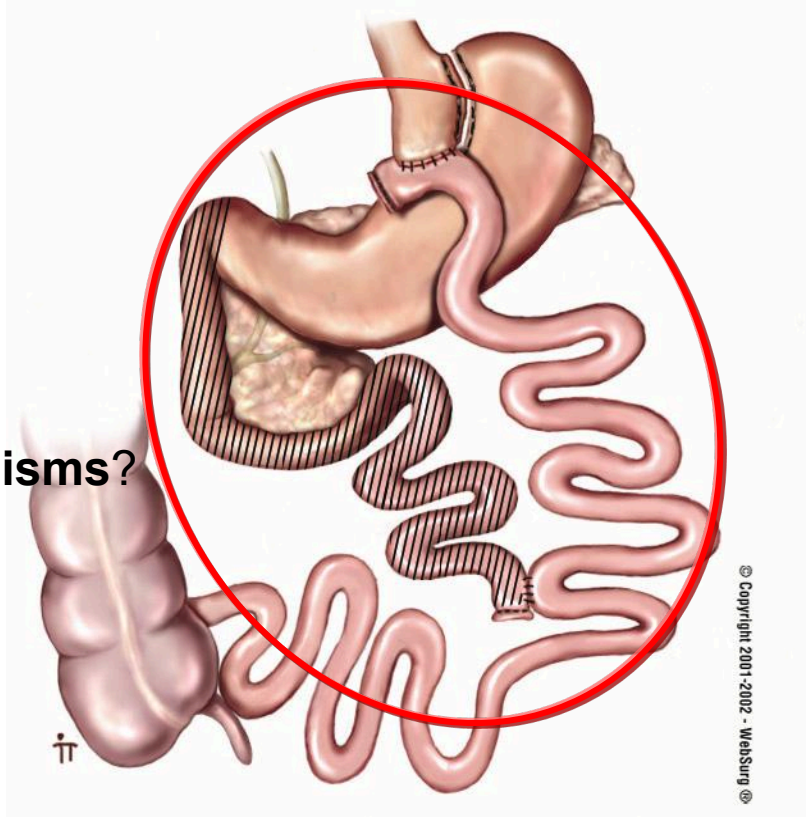
Changes in gut microbiota ?

Alterations in bile acid metabolism?

Changes in nutrient sensing mechanisms?

Anti-incretins?

Others?



Is Type 2 Diabetes an Operable Intestinal Disease?

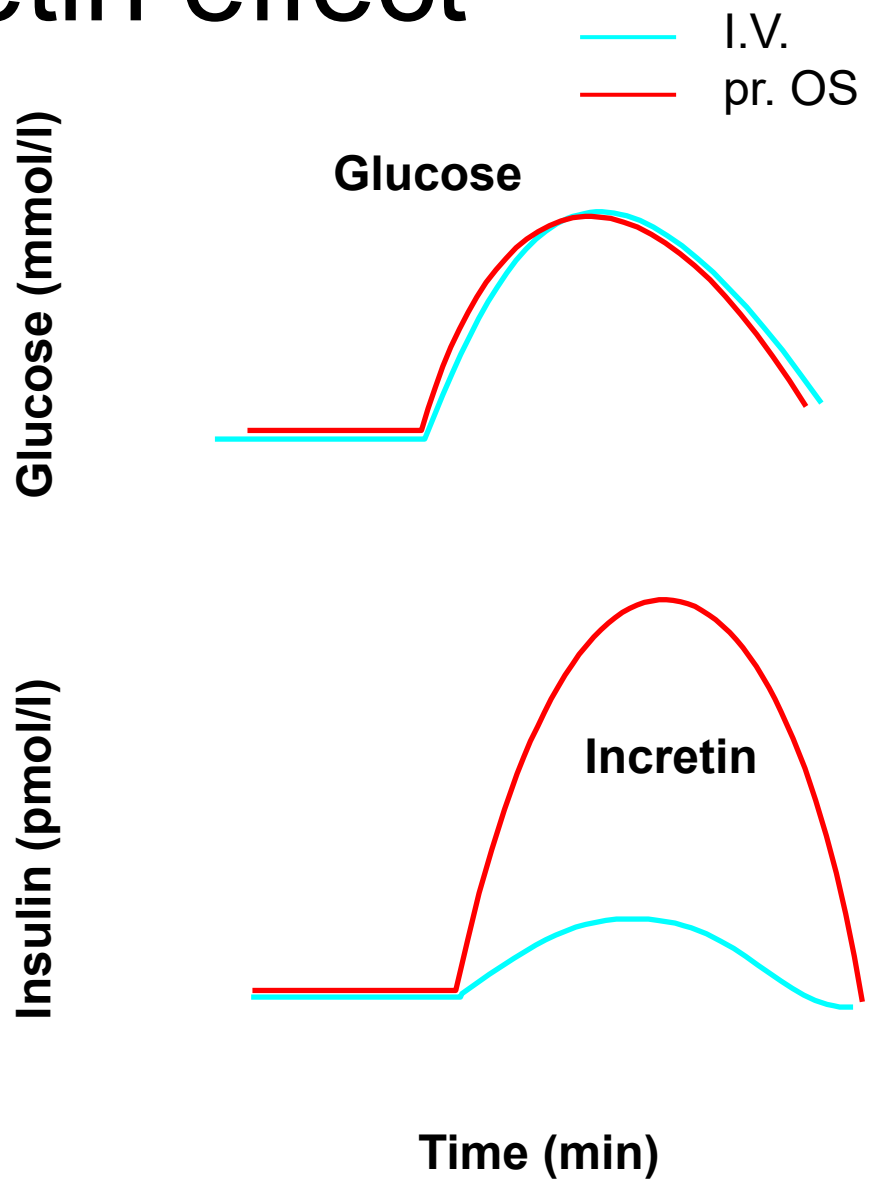
A provocative yet reasonable hypothesis

FRANCESCO RUBINO, MD

TYPE 2 DIABETES: IS IT AN INTESTINAL DISEASE? — The rapid resolution of diabetes after Roux-

The incretin effect

- 70% of post-glucose insulin secretion is due to the incretin effect
- The incretin effect is due to gut hormones;



Glucose Lowering Mechanisms in the Postprandial State

Nutrients Passage in the GI Tract Induces:

- Suppression of ghrelin
- Increase in GLP-1/GIP
- Suppression of Glucagon
- Increase in Insulin

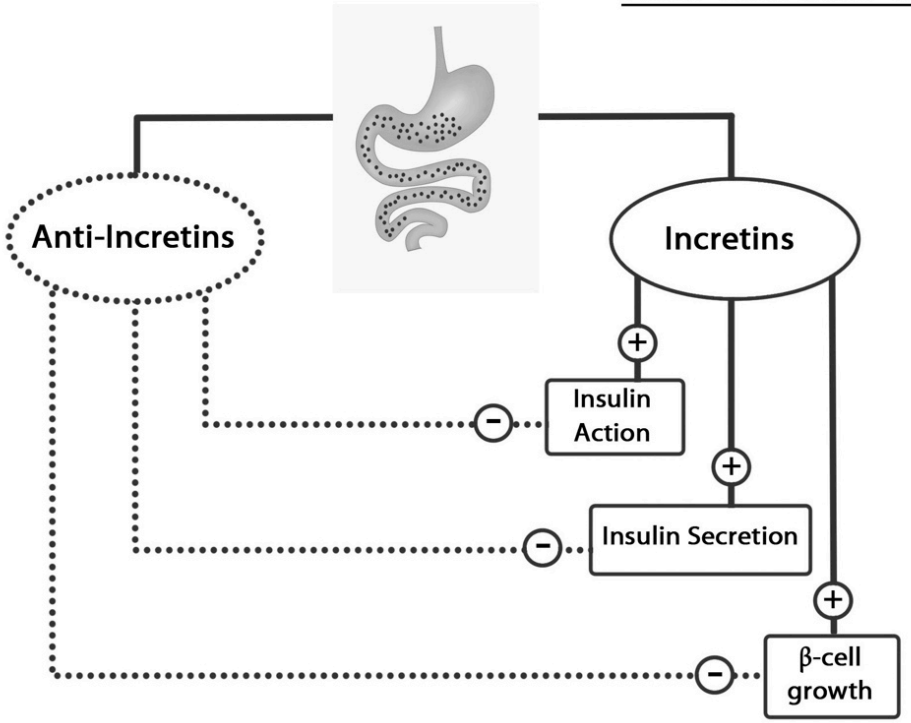
- Reduction of hepatic glucose production (nutrient sensing) (Lam et al, Nature)
- Increased intestinal glucose uptake (Stilopulous et al Science 2013)

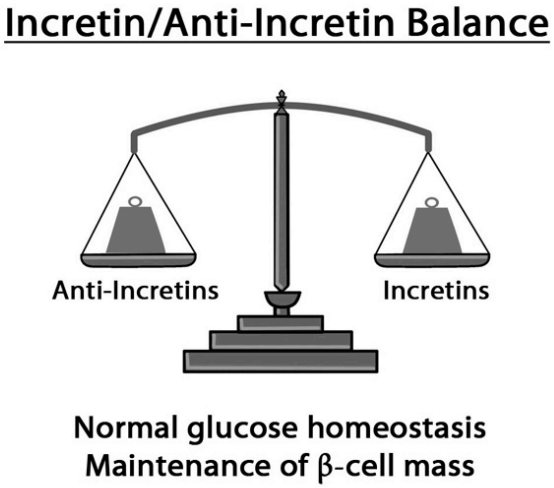
>>> GLUCOSE LOWERING EFFECT

Anti-incretin Theory

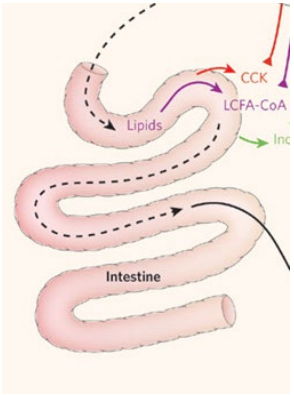
(Ann Surg 2002; Ann Surg 2004; Diabetes Care 2009; Nature Rev Endo 2010; Diabetes July 2014)

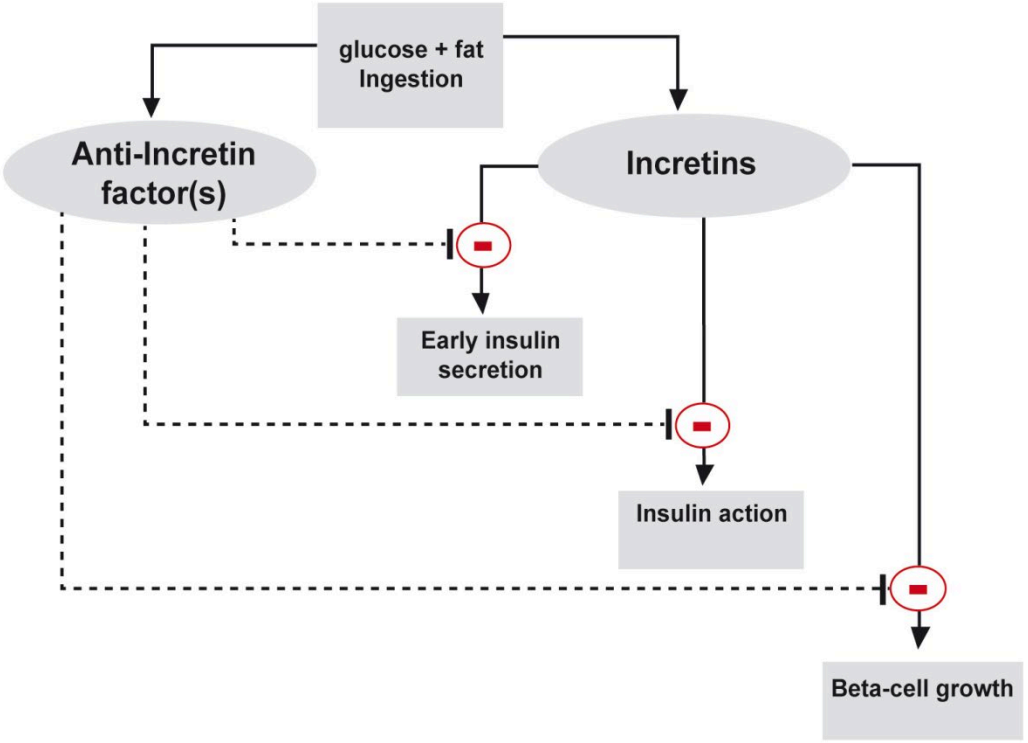
A





The Anti-Incretin Theory

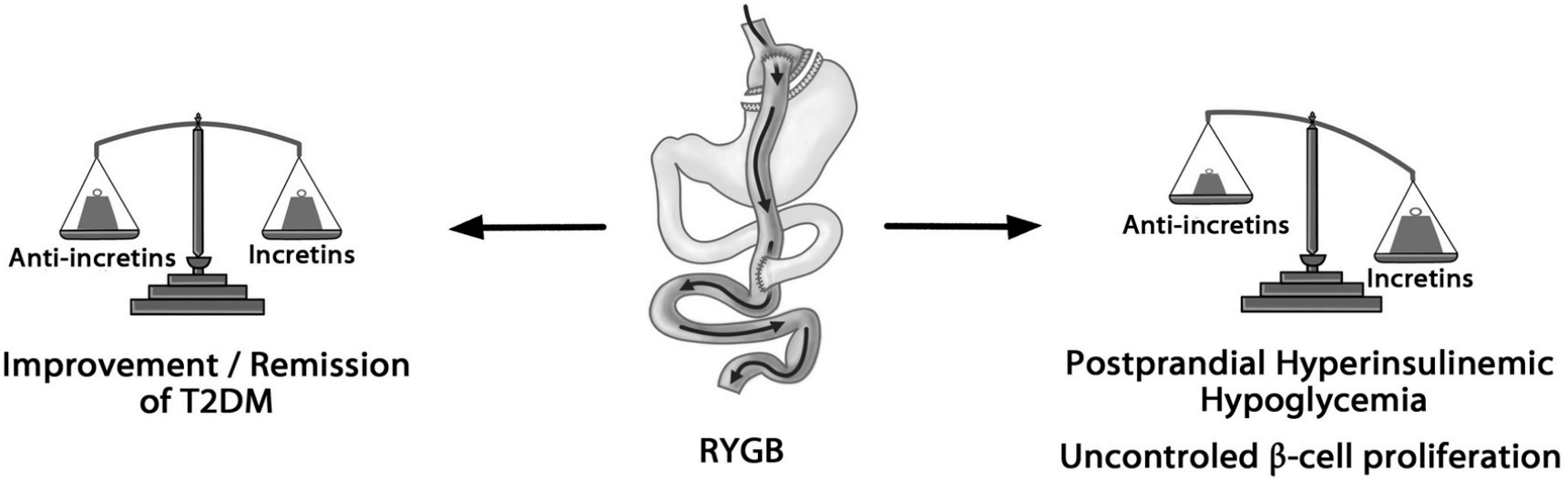




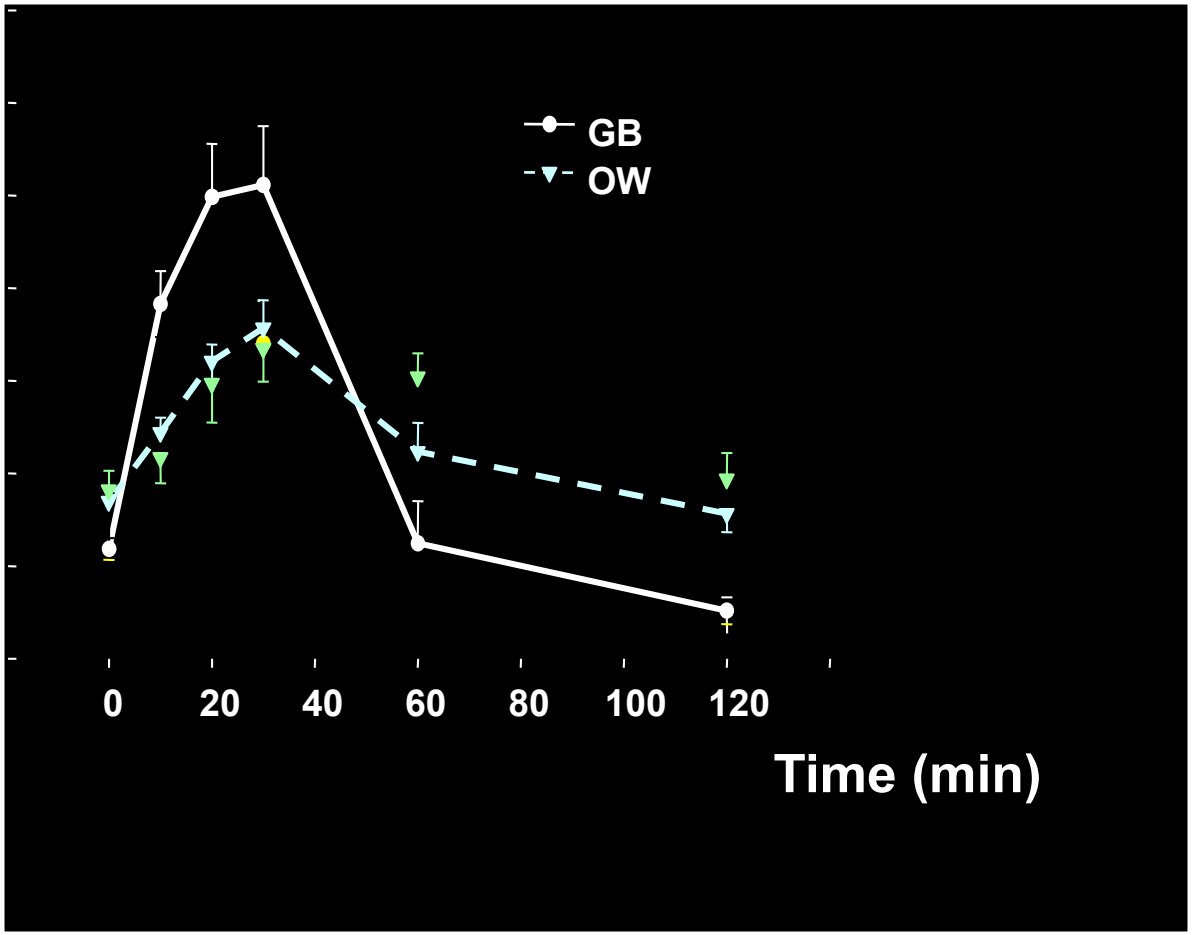
Foodborne stimuli may cause exaggerated/untimely activation of anti-incretin mechanisms, which may act as a diabetogenic factor

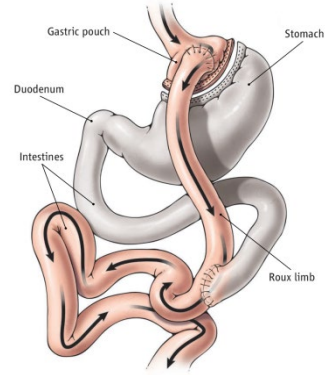
Anti-incretin Theory may Explain Benefits and Complications of RYGB

C

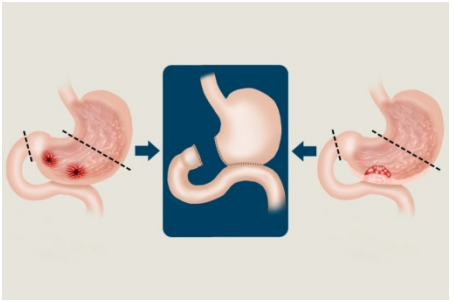


Glucose Excursions after Alterations of GI Anatomy Suggest Disruption of Physiologic Incretin/Anti-Incretin Balance





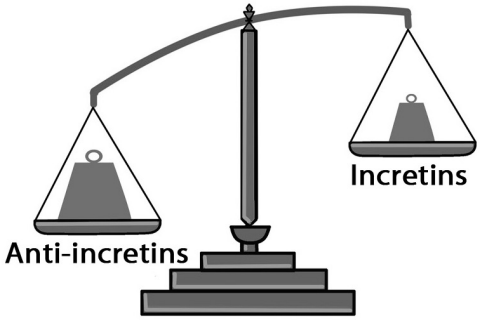
Post-RYGB



Post-gastrectomy

Predictions

Too Much Anti-Incretin



Insulin resistance
Impaired β-cell function
β-cell depletion

(Type 2 Diabetes)

Excess anti-incretin results in IR and/or beta-cell Dysfunction/depletion

>> gut factors from subjects with IR or diabetes should be able to induce IR in normal cells/subjects

Jejunal Proteins Secreted by db/db Mice or Insulin- Resistant Humans Impair the Insulin Signaling and Determine Insulin Resistance

S. Salinari, C. Debard , A. Bertuzzi , C. Durand, P. Zimmet, H. Vidal, G. Mingrone

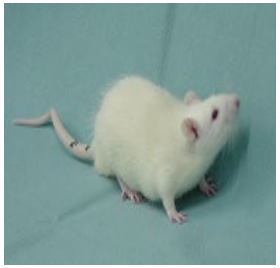
PLOS ONE 2013

Proteins from duodenum-jejunum of diabetic mice (db/db)

Normal Mice Soleus Muscle

L-cells skeletal muscle

➢ **Insulin Resistance**



Normal, Swiss Mice

Intraperitoneal Insulin Tolerance Test IPITT

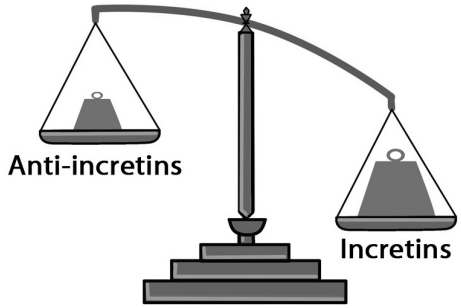
➢ **Reduced Insulin Sensitivity (minimal model)**

Predictions

incretin/anti-incretin balance ensures control of beta-cell proliferation/growth

- **Uncoupling or net reduction of anti-incretin mechanisms by disruption of GI anatomy can cause beta-cell proliferation**

Not Enough Anti-Incretin



Postprandial hyperinsulinemic hypoglycemia
Uncontrolled β-cell proliferation

Beta-Cell Proliferation after RYGB/DJB Suggests Disruption of Physiologic Regulation of Beta-Cell Growth

RYGB vs Sham Operation in non diabetic anumals (pigs)

RYGB > Increased in β-cell mass,
Increased islet number
increased number of extraislet β-cells

Lindqvist et al; Diabetes May 2014 63:5 1665-1671

Decreased beta-cell loss in GK rats after DJB
(Speck M et al; Am J Phys End Met 2011)

Nesidioblastosis after RYGB in humans
(Service et al; NEJM 2005)

Heterotopic (gastric) pancreatic mass after RYGB in humans
(Guimares et al; BMC Surg 2013)

Diabetes Volume 63, ■■■ 2014

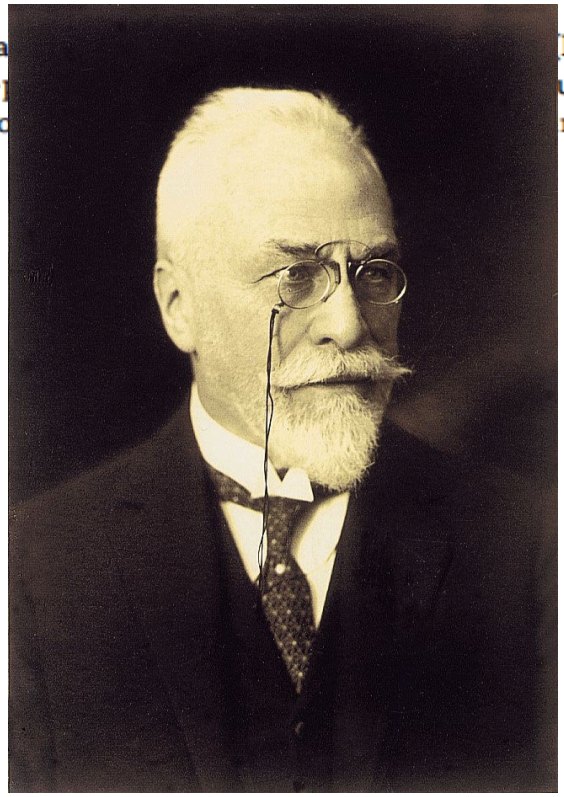
Francesco Rubino and Stephanie A. Amiel

Is the Gut the "Sweet Spot" for the Treatment of Diabetes?

Diabetes 2014;63:1–4 | DOI: 10.2337/db14-0402

Oskar Minkowski possessed a rare combination of talents: He was an internist with the intuition of a scientist and the dexterity of a surgeon. One day in 1889, he and his

In pa (RYGB) restores first- ults in hyperse- cretic ng nutrient in-



Diabetes, July 2014, in press

3rd World Congress on Interventional Therapies for Diabetes
&
2nd Diabetes Surgery Summit (DSS)

Joined Event

LONDON, UK
SEPTEMBER
2015

the most important event

in *Diabetes and Metabolic Surgery*

More to come…

Acknowledgements

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